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Combined Action and Potentation of Clostridium Toxins

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COMBINED ACTION AND POTENTIATION OF CLOSTRIDIUM TOXINS

by

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Abstract: If previously mixed and held at 37°C for 45 min Clostridium perfringens and Cl. histolyticum become more toxic. This shows up as depression of the absorptive function of the liver and spleen reticuloendothelial system and increase in hemolytic and lethal effect. This may explain the high incidence of fatalities in gas infections from these bacteria.

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COMBINED ACTION AND POTENTIATION OF CLOSTRIDIUM TOXINS

Mikrobiologichnyy zhurnal
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A. I. Mitskevych

Gas infection as a rule is a polymicrobic disease in which the combination of the two causative agents, Clostridium perfringens and Clostridium histolyticum, substantially complicates the clinical picture and raises the percentage of fatalities [1-6].

Until recently research on microbe associations in gas infection was conducted mainly in the direction of studying the effect of the associating microbes on each other and and the requisite attention was not devoted to the interaction of their toxins.

It has been established in the literature [7-15 etc.] that when the toxins of certain species of anaerobes, as well as of the toxins of these excitants and of particular species of aerobes, operate together they are seen to become potentiated.

Among the microbe associations which cause gas gangrene the combined action of the toxins of Cl. perfringens and of Cl. histolyticum is the least studied. In view of this we set ourselves the task of studying potentiation of these toxins during their combined action on the animal organism and under in vitro experimental conditions.

To clarify this phenomenon experiments were conducted on the effect of Cl. perfringens and Cl. histolyticum toxins on the function of the reticuloendothelial system, as well as on the change in the hemolytic and lethal activity of these toxins when they act together.

The first series of experiments utilized dry Cl. perfringens toxins of the series 16 and 1:10-52 and dry Cl. histolyticum toxin of series 16 obtained from the Institute of Epidemiology and Microbiology imeni M.F. Gamaley with which 18 rabbits and 120 white mice were infected. The toxins and their mixtures were injected in subtotal doses

both directly after preparation thereof and after having been kept in a thermostat at 37°C for 45 min. Inactivated toxins were injected into the control animals.

Blocking action from subtotal doses of toxins and their mixtures on cells of the reticuloendothelial system of the liver and spleen was detected in rabbits and white mice to an almost identical degree (Table I). At the same time a difference was observed in the poisonous properties of the toxins injected. It was most pronounced in the Cl. histolyticum toxin and exceeded the analogous action of the rest of the toxins by a factor of two or three. This is particularly apparent when the toxin is kept in the thermostat at 37°C for 45 min. Mixing the toxins of Cl. perfringens and Cl. histolyticum and then holding them in the thermostat for 45 min causes a four to sixfold rise in their poisonous properties over those of other toxins, with the exception of Cl. perfringens and Cl. septicum.

Besides a study of the effect of Cl. perfringens and Cl. histolyticum toxins on the reticuloendothelial system, research was carried out on the hemolytic and lethal properties of these toxins. Potentiation of the toxins of Cl. perfringens and Cl. histolyticum was studied in in vitro experiments -- 21 series -- and in experiments on 8 rabbits, 10 guinea pigs, and 207 white mice. The experiments made use both of the indicated series of dry toxins and the natural toxins of Cl. perfringens strain 235 and Cl. histolyticum strain 5. It has been established that the hemolytic action of the Cl. perfringens and Cl. histolyticum toxins increases substantially if, after mixing, they are kept in a thermostat for 45 min at 37°C (Table II). This is corroborated by experiments with a background dose of each of these two toxins. The hemolysis reactions were set up in a volume of 1,5 cc, of which 1 cc comprised the toxins in a 0,85% solution of sodium chloride and 0,5%, a 5% suspension of leporine erythrocytes. Holding the toxin of Cl. perfringens at 37°C for 45 min strengthened its hemolytic properties. This is especially apparent when potentiating the toxins of Cl. perfringens and Cl. histolyticus, where a four to eightfold intensification was observed.

A rise in hemolytic activity in the potentiation of toxins of Cl. perfringens and Cl. histolyticum became evident as increased lethal action in experiments on animals. This applies in equal measure to rabbits, guinea pigs, and white mice (Table III). Analysis of the data indicates that the toxins mentioned intensify their lethal properties when they are kept at a temperature of 37°C for 45 min. This intensification becomes considerably greater (by a factor of four to eight) if they have been previously mixed and so held before being injected into the animals. Similar results were obtained in experiments on rabbits and guinea pigs.

TABLE I. Comparative Data on Effect of Toxins of Causative Agents of Gas Infection on Reticuloendothelial Cells of the Liver and Spleen

(a) Назва токсинів	(b)	(c)	(d)	(e)	(f) (g) Контроль	(h) Токсини: не нагріваними (i)	нагрітими (j)
Cl. perfringens	[illegible]	(k) Кролики	3	Печінка (m)	52,2	14,7	8,7
				Селезінка (n)	41,9	15,8	9,8
	0,9	(l) Миші	12	Печінка (m)	35,4	5,9	3,9
				Селезінка (n)	39,2	6,1	4,7
Cl. septicum	30	(k) Кролики	3	Печінка (m)	57,5	12,3	12,1
				Селезінка (n)	56,3	14,2	13,8
	0,9	(l) Миші	12	Печінка (m)	39,0	15,4	15,0
				Селезінка (n)	39,6	15,7	15,4
Cl. oedematiens	30	(k) Кролики	3	Печінка (m)	52,7	19,1	19,0
				Селезінка (n)	50,6	18,6	18,1
	0,9	(l) Миші	12	Печінка (m)	31,1	14,8	14,0
Cl. histolyticum	30	(k) Кролики	3	Печінка (m)	49,6	7,5	4,7
				Селезінка (n)	51,5	7,1	5,2
	0,9	(l) Миші	12	Печінка (m)	32,7	9,7	5,5
				Селезінка (n)	36,4	9,9	6,1
(o) Суміші токсинів							
Cl. perfringens i septicum	15	(k) Кролики	3	Печінка (m)	47,9	4,8	1,4
	15			Селезінка (n)	49,2	5,2	1,7
	0,45	(l) Миші	12	Печінка (m)	39,5	5,7	2,3
	0,45			Селезінка (n)	38,4	5,4	2,7
Cl. perfringens i histolyticum	15	(k) Кролики	3	Печінка (m)	40,4	5,8	1,9
	15			Селезінка (n)	49,6	6,1	2,3
	0,45	(l) Миші	12	Печінка (m)	37,5	6,8	3,9
	0,45			Селезінка (n)	38,5	6,9	3,4
Cl. perfringens i oedematiens	0,45	»	12	Печінка (m)	40,7	7,9	5,4
	0,45			Селезінка (n)	41,4	8,3	5,8
Cl. septicum i oedematiens	0,45	»	12	Печінка (m)	37,6	18,5	18,1
	0,45			Селезінка (n)	37,7	20,4	20,0
Cl. oedematiens i histolyticum	0,45	»	12	Печінка (m)	40,4	19,7	16,1
	0,45			Селезінка (n)	39,7	20,1	16,4
Cl. septicum i histolyticum	0,45	»	12	Печінка (m)	37,9	15,4	12,7
	0,45			Селезінка (n)	37,4	16,5	12,9

Key: (a) Toxin name, (b) MLD (for mice) injected in animals, (c) Experimental animals, (d) Number, (e) Organs studied, (f) Number of ink in reticuloendothelial cells, (g) Control, (h) Toxins, (i) Not heat-treated, (j) Heat-treated, (k) Rabbits, (l) Mice, (m) Liver, (n) Spleen, (o) Toxin mixes

TABLE II. Intensification in Hemolytic Properties of Toxins of Cl. perfringens and Cl. histolyticum When Kept in Thermostat for 45 min

(a) Токсини (в мл)				(f) Облік реакції гемолізу через 2 год
(b) не витримані		(c) витримані		
Cl. perfringens (d) серія 1:10	Cl. histolyticum (e) серія 16	Cl. perfringens (d) серія 1:10	Cl. histolyticum (e) серія 16	
0,4				+++
0,3				+
0,2				+—
0,1				+—
0,05				—
	0,4			+++
	0,3			+
	0,2			+—
	0,1			—
		0,4		++
		0,3		+++
		0,2		+
		0,1		+
		0,05		+—
		0,025		—
			0,4	++
			0,3	+
			0,2	+—
			0,1	—
		0,2	0,2	++++
		0,1	0,1	+++
		0,05	0,05	++
		0,025	0,025	+
		0,012	0,012	—

Key: (a) Toxins in cc, (b) Not heat-treated, (c) Heat-treated, (d) Series 1:10, (e) Series 16, (f) Estimate of hemolytic reaction in 2 hr

Conclusions

1. In the combined action of the toxins of Cl. perfringens and Cl. histolyticum is observed a potentiation of their poisonous effect, whose strength rises if the toxin mixture is previously exposed at 37°C for 45 min.

2. The potentiation of the toxins, particularly of Cl. perfringens and Cl. histolyticum, makes itself manifest in drastic depression of the absorptive function of the cells of the reticuloendothelial system of the liver and spleen and in rise in the hemolytic and lethal activity.

3. Potentiation of the toxins and intensification of their poisonous properties may explain the severity of the clinical picture and high percentage of fatalities in gas infection caused by Clostridium

TABLE III. Effect of Potentiation of Cl. perfringens and Cl. histolyticum Toxins on Their Lethal Properties

(a) Токсини (в DLM)				(d) Результати досліда		
(b) не витримані		(c) витримані		(e) Заражено	(f) Загинуло	(g) Живі
Cl. perfringens	*Cl. histolyticum*	*Cl. perfringens*	*Cl. histolyticum*			
1				12	12	0
0,75				12	0	12
	1			12	12	0
	0,75			12	0	12
		1		12	12	0
		0,75		12	7	5
		0,5		12	4	8
		0,25		12	0	12
			1	12	12	0
			0,75	12	3	9
			0,5	12	0	12
0,5	0,5			12	12	0
0,25	0,25			12	0	12
		0,5	0,5	12	12	0
		0,25	0,25	12	11	1
		0,12	0,12	12	9	3
		0,06	0,06	12	2	10
		0,03	0,03	12	2	10
		0,015	0,015	12	0	12

Key: (a) Toxins in MLD, (b) Not heat-treated, (c) Heat-treated, (d) Experimental results, (e) Infected, (f) Died, (g) Lived

perfringens and Clostridium histolyticum.

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